D-Psicose, a Sweet Monosaccharide, Ameliorate Hyperglycemia, and Dyslipidemia in C57BL/6J *db/db* Mice

S.H. Baek, S.J. Park, and H.G. Lee

ABSTRACT: D-psicose has been implicated in glycemic control in recent animal and human studies. In this study, the effects of D-psicose on glycemic responses, insulin release, and lipid profiles were compared with those of D-glucose and D-fructose in a genetic diabetes model. C57BL/6J *db/db* mice were orally supplemented with 200 mg/kg BW of D-psicose, D-glucose, or D-fructose, respectively, while diabetes control or wild type mice were supplemented with water instead. D-psicose sustained weight gain by about 10% compared to other groups. The initial blood glucose level maintained from 276 to 305 mg/dL during 28 d in the D-psicose group, whereas a 2-fold increase was found in other groups ($P < 0.05$) among diabetic mice. D-psicose significantly improved glucose tolerance and the areas under the curve (AUC) for glucose among diabetes ($P < 0.05$), but had no effect on serum insulin concentration. The plasma lipid profile was not changed by supplemental monosacchrides, although the ratio of LDL-cholesterol/HDL-cholesterol was ameliorated by D-psicose. The administration of D-psicose reversed hepatic concentrations of triglyceride (TG) and total cholesterol (TC) by 37.88% and 62.89%, respectively, compared to the diabetes control ($P < 0.05$). The current findings suggest that D-psicose shows promise as an antidiabetic and may have antidyslipidemic effects in type 2 diabetes.

Keywords: C57BL/6J *db/db* mice, D-fructose, D-glucose, D-psicose, type 2 diabetes

Introduction

D-Psicose (D-*ribo*-2-hexulose, C-3 epimer of D-fructose, molecular weight 180.156) originates from wheat, *Itea* plants, processed cane and beet molasses (Binkley 1963; Miller and Swain 1965). It is also present in commercial complexes of D-glucose and D-fructose in small quantities (Cree and others 1968). Oshima and others (2006) reported that D-piscose, corresponding to 70% of the sweet taste of sucrose, is formed from fructose during cooking and is included in fruit juice, sauce and other foodstuffs.

Due to the rarely existing natural hexose, the biological functions and pathophysiological implications of D-psicose have not been fully explored. However, methods of mass-producing D-psicose have lately been developed using isomerase and D-tagatose 3-epimerase. These innovations have enabled a number of investigations to be performed (Granstrom and others 2004; Gullapalli and others 2007; Murao and others 2007).

Regarding safety, the LD50 value has been evaluated at 16 g/kg in rats (Matsuo and others 2002b). Maximum noneffective level of D-psicose was estimated about 0.55 g/kg body weight in human gastrointestinal environment (Iida and others 2007).

D-psicose has attracted much attention recently for promising use as an inhibitor of hepatic lipogenic enzymes (Matsuo and others 2001a), as a no-energy sweetener (Matsuo and others 2002a), as a stimulator of insulin secretion (Murao and others 2004), and as an activator of abdominal fat loss (Matsuo and Izumori 2006a). Specifically, in rats, 5% supplemental D-psicose decreased diurnal plasma glucose level and increased plasma insulin concentration (Matsuo and Izumori 2006a). In healthy humans, postprandial blood glucose and insulin concentrations were suppressed by the administration of D-psicose (>5 g) (Iida and others 2008). These results have proposed that D-psicose can be an appropriate candidate for antidiabetic agent or food ingredient, because good control of blood glucose and insulin concentration is the key step in preventing and reversing diabetes. Moreover, there has been limited efficacy and adverse side effects of currently available therapies on diabetes (Pratley 2009).

In this study, we examined the effects of oral D-psicose on blood glucose and lipid profile in C57BL/6J *db/db* mice and confirmed the antidiabetic and antidyslipidemic effects.

Materials and Methods

Preparation of D-psicose

D-Psicose was donated by the Dept. of Bioscience and Biotechnology, Konkuk Univ., Seoul, Korea). Briefly, D-psicose was generated by the bioconversion of D-fructose into D-psicose via the D-psicose 3-epimerase (15 U of enzyme) using the jar fermentor (Korea Fermentor Co., Incheon, Korea). The interconversion between D-gluocse, D-fructose, and D-psicose catalyzed by D-xylose iosmerase and D-tagatose 3-epimerase, respectively is schematically shown in Figure 1. The inoculum was transferred into the fermentor containing 70% D-fructose then incubated at 50 °C for 24 h. The mixtures of D-fructose and D-psicose were separated by a medium pressure liquid chromatography system (Yamazen YFLC 700, Tokyo, Japan), applied to open column (Diaion UBK 235) and it was filtered (0.45 μm) and concentrated using an evaporator. The concentrations of D-psicose and D-fructose were analyzed by high-performance liquid chromatography (HPLC) system

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(Shimadzu SCL-10A, Kyoto, Japan) with a Shimadzu RID-10A detector and a BP-100 Ca^{2+} carbohydrate column (Benson Polymeric Inc. Reno, Nev., U.S.A.) (Oh and others 2007). The 20 μL sample was injected into the column and eluted with water at 80 °C with a constant flow rate of 0.4 mL/min for 15 min. The purity of D-psicose in this study was above 97% as confirmed by HPLC. Sugars (D-fructose and D-glucose) and all other chemicals were of analytical grade, which were obtained from Sigma-Aldrich Chemical Company (St. Louis, Mo., U.S.A.).

Animals and experimental diets

All procedures involving animals were approved by the Experimental Animal Care Committee of Hanyang Univ., Seoul, Korea. Male C57BL/6J *db/db* mice (6-wk old, $n = 40$) and the paired wild type mice ($n = 10$) were obtained from Central Lab Animal Inc. (Seoul, Korea). They were housed at 22 ± 2 °C with a 12 h light/dark cycle. They were acclimatized for 7 d before experiments to have free access to standard pellet chow diets and water except on the overnight fast before the oral glucose tolerance test (OGTT) on day 28. The *db/db* mice were randomly divided into 4 groups: diabetic control (DC), D-psicose (DP), D-glucose (DG), and D-fructose (DF). Two control groups, DC and normal control (NC), were orally provided with 200 μL distilled water instead of individual monosaccharide supplement (200 mg/kg body weight). The concentration of sugars used in this study was determined as minimal dosage producing antidiabetic effect based on preliminary dose-response study using 100, 200, and 400 mg/kg body weight (data not shown). Vitamin and mineral mixtures based on the N-93 Diet (New Brunswick, N.J., U.S.A.) were used. The food consumption and body weight were measured every week, respectively. Feeding efficiency ratio (FER) was calculated as follows: feeding efficiency ratio (%) = body weight gain (g/d) /food intake (g/d) × 100.

Preparations of blood, liver, and fecal samples

On day 28, animals were deprived of food for 12 h and blood was collected for lipid compositions analysis from the abdominal aorta under dry ice anesthesia. It was incubated at room temperature for 45 min, and centrifuged at 4000 *g* for 15 min at 4 °C and frozen at −70 °C until analyzed. The liver was excised and immediately weighed and washed with ice-cold isotonic saline then stored at −70 °C for laboratory analysis. Feces were collected during the last 3 days of the experimental periods and oven-dried at 80 °C for 24 h then stored at −20 °C until analysis.

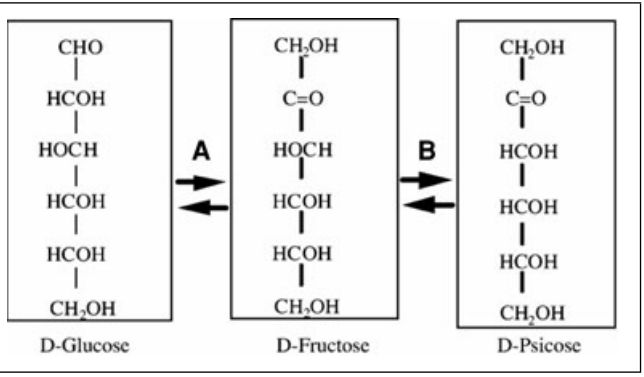

Figure 1—Interconversion between D-glucose, D-fructose, and D-psicose. D-xylose isomerase (A); D-tagatose 3 epimerase (B).

Plasma glucose and insulin concentrations and oral glucose tolerance test (OGTT)

Blood samples were collected from the tail vein every morning 2 times a week for 28 d to evaluate the effect of various monosaccharide intakes using a commercial kit (Dongbang Intl. Co., Seoul, Korea).

At the end of the experimental period, 10 mice were subjected to an OGTT. Briefly, after overnight fasting, blood was collected from the tail vein prior to and 30, 60, 90, and 120 min after glucose administration (2 g/kg). Plasma glucose was measured using a commercial kit (Dongbang Intl. Co.). Serum insulin was determined by enzyme immunoassay kit (Shibayaki Co., Shibukawa, Japan). Total areas under a curve (AUC) for glucose were calculated.

Measurement of lipid compositions in plasma, liver, and feces

Lipid was extracted from plasma, liver, and feces, respectively, according to the method of Folch and others (1957). The concentrations of serum triglyceride (TG), total cholesterol, HDL-cholesterol, and LDL-cholesterol were measured by blood chemistry analyzer (Olympus AU 400, Japan). Hepatic and fecal lipids were measured by enzymatically using a commercial kit (Asan Pharmaceutical Co., Seoul, Korea) based on a modification of lipase–glycerol phosphate oxidase method (Allain and others 1974; McGowan and others 1983).

Statistical analysis

Results were expressed as means ± SD and the differences were determined by one-way analysis of variance (ANOVA) using SPSS 12.0 program (SPSS Inc., Chicago, Ill., U.S.A.). Group comparisons were performed using variance analysis followed by Duncan's multiple range test. Statistical significance was accepted at $P < 0.05$.

Results and Discussion

Effect of dietary D-psicose on body weight

There were no significant inter-group differences on the initial body weight and the food intake per day (Table 1). In contrast, weight gain was significantly lower in the D-psicose group than in the D-glucose, D-fructose group, or even in the diabetic control group during 28 d ($P < 0.05$ for each, Table 1). The food efficiency ratio was thus lower in the D-psicose group compared to that of in other monosaccharide-supplemented groups in *db/db* mice ($P < 0.05$, Table 1). These results were in the accordance with previous study. Mastuo and others (2001b, 2002a) provided evidence that D-psicose supplementation reduced body fat accumulation compared to D-fructose because no energy was provided by D-psicose. They also suggested that the lower lipogenic enzyme activity, such as fatty acid synthase and glucose 6-phosphate dehydrogenase, in the liver result in the lower abdominal fat accumulation in rat fed D-psicose (2001a). The current result therefore confirmed that D-psicose might have a weight loss potential on obesity and diabetes, although the underlying mechanisms should be further studied.

Effect of dietary D-psicose on blood glucose and serum insulin level

Dietary D-psicose was screened for its *in vivo* antidiabetic activity in diabetes mice. The *db/db* mice, a well-characterized model of obesity and type 2 diabetes, display hyperglycemia, hyperinsulinemia, and glucosuria. The optimal age of *db/db* mice as diabetes model is from week 12 to 18 (Kumar and others 2009). The *db/db* mice fed high fat diet (60% of energy) delineated the phenotypic

Table 1 — Effects of D-psicose supplementation on body weight, food intake, and serum insulin concentration in C57BL/6J *db/db* mice.

	NC	DC	DP	DG	DF
Initial BW (g)	22.38 ± 1.06[1,ns]	25.00 ± 2.07	25.13 ± 1.51	25.13 ± 3.18	25.00 ± 1.58
Final BW (g)	25.13 ± 1.12[bc]	32.50 ± 1.51[a]	29.88 ± 1.35[b]	33.00 ± 2.26[a]	32.63 ± 1.40[a]
Weight gain (g/d)	2.75 ± 1.75[c]	7.50 ± 2.63[a]	4.75 ± 1.48[b]	7.87 ± 4.01[a]	7.63 ± 1.45[a]
Food intake (g/d)	4.77 ± 0.98[ns]	5.13 ± 0.49	4.71 ± 0.75	5.11 ± 0.85	5.21 ± 0.82
Food Efficiency Ratio	0.57 ± 0.02[c]	1.46 ± 0.01[a]	1.00 ± 0.09[b]	1.54 ± 0.02[a]	1.46 ± 0.04[a]
Insulin level (ng/mL)	6.41 ± 0.71[a]	6.20 ± 0.94[a]	2.99 ± 1.47[b]	5.89 ± 1.14[a]	5.03 ± 0.61[a]

[1] Values are mean ± S.E. of 10 measurements in each group.
Means with different superscripts within a row are significantly different ($P < 0.05$, one-way ANOVA).
NC = normal control; DC = diabetic control; DP = diabetic mice fed supplemental D-psicose; DG = diabetic mice fed supplemental D-glucose; DF = diabetic mice fed supplemental D-fructose; ns = not significant.

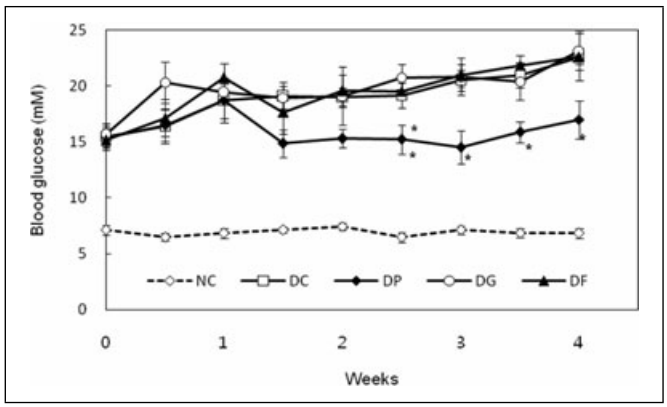

Figure 2 — Effects of D-psicose supplementation on postprandial plasma glucose concentration in C57BL/6J *db/db* mice. Values are mean ± S.E. of 10 measurements in each group. Statistically significant differences between supplements are indicated at *$P < 0.05$. To convert mM glucose to milligrams per deciliter, multiply by 18. NC, normal control; DC, diabetic control; DP, diabetic mice fed D-psicose; DG, diabetic mice fed D-glucose; DF, diabetic mice fed D-fructose; DC and NC were orally provided by 200 μL distilled water instead of individual monosaccharides (200 mg/kg body weight).

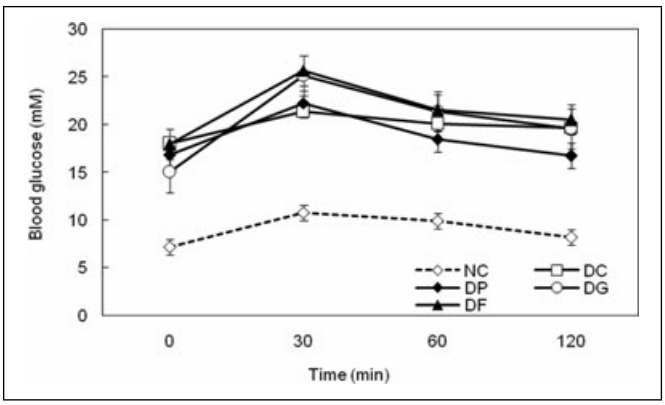

Figure 3 — Effects of D-psicose supplementation on glucose tolerance test in C57BL/6J *db/db* mice. Values are mean ± S.E. of 10 measurements in each group. To convert mM glucose to mg/dL, multiply by 18. NC, normal control; DC, diabetic control; DP, diabetic mice fed D-psicose; DG, diabetic mice fed D-glucose; DF, diabetic mice fed D-fructose; DC and NC were orally provided by 200 uL distilled water instead of individual monosaccharide (200 mg/kg body weight).

and metabolic components of metabolic syndrome (Catherine and others 2007).

In this study, the initial concentration of blood glucose in diabetic mice was 2-fold higher (15.45 ± 2.78 mM) than that of normal control mice (7.13 ± 1.17 mM) (Figure 2). There were no significant inter-group differences in diabetic mice on the baseline concentration of blood glucose. Postprandial blood glucose was gradually increased in all diabetes models during 28 d. In contrast, the D-psicose group showed lowering blood glucose profiles compare to the D-glucose, D-fructose group, and the control group in *db/db* ($P < 0.05$, Figure 2). Similar to our results, Matsuo and others (2006) found that the ingestion of D-psicose significantly restricted postprandial blood glucose raise in Wistar rats. The present finding, therefore, fortified the antihyperglycemic effect of D-psicose even on the transgenic diabetes model.

The extracellular concentration of glucose is maintained within a very narrow range through the tightly coordinated secretion of insulin and glucagons in normal physiology (Bosch and others 1998). Contrary to expectations, our transgenic mice did not show hyperinsulinemia compared to the wild type mice. This report is insufficient to elucidate whether D-psicose influences insulin secretion due to the lack of initial insulin levels. Neither D-glucose nor D-fructose significantly affected serum insulin concentration during 28 d. Interestingly, the D-psicose group have shown approximately 2-fold lowered serum insulin value compared to the control group after supplementation ($P < 0.05$) (Table 1). The comparable results were shown by Matsuo and others (2001a). Serum insulin concentration was not significantly different among the cellulose, glucose, fructose and psicose supplement groups in Wistar rats. They speculated that the results could be from sacrifice at overnight fasting or 5% supplementation of test carbohydrates. Alternatively, it might be due, at least in part, to certain components in D-psicose being responsible for reducing the blood glucose elevation since the rare sugar has been absorbed poorly in the digestive tract, as previously reported (Matsuo and others 2001b).

Effect of dietary D-psicose on glucose tolerance test

Figure 3 showed the result of the OGTT in the 2 control groups and in the D-glucose, D-fructose, and D-psicose groups. Glucose intolerance was observed in all *db/db* mice expectedly, most pronounced in the D-glucose and D-fructose groups. Plasma glucose levels peaked at 30 min after a glucose challenge in all groups. Both the D-glucose and the D-fructose groups induced the highest peaks with similar blood glucose kinetics. In contrast, the D-psicose group maintained the lower peak with similar blood glucose kinetics of the diabetic control group (Figure 3). The AUC for plasma glucose in the D-psicose group was 22.8% and 20% less than in the D-glucose and the D-fructose group, and 15% less than the control group in *db/db* mice. These results are in good agreement with those described by Matsuo (2006). D-psicose maintained plasma glucose and serum insulin concentrations during OGTT similar to those of cellulose groups until 8 and 16 wk. Moreover, D-psicose significantly inhibited the increment of plasma glucose concentration induced by sucrose and maltose. Therefore, this

Table 2— Effects of D-psicose supplementation on fasting lipid profile in plasma and liver and fecal lipids excretion in C57BL/6J *db/db* mice.

	NC	DC	DP	DG	DF
Plasma (mg/dL)					
Triglyceride	82.89 ± 8.00[1]	158.77 ± 79.71^{ns}	233.46 ± 70.39	218.13 ± 91.50	203.99 ± 68.59
Total cholesterol	115.17 ± 15.74	263.66 ± 56.16^{ns}	254.06 ± 36.82	253.16 ± 37.71	255.16 ± 34.41
HDL-C	73.13 ± 8.91	101.88 ± 32.60^{ns}	118.00 ± 30.23	120.00 ± 14.25	107.25 ± 30.44
LDL-C	25.47 ± 20.68	130.03 ± 49.92^{ns}	89.36 ± 38.84	89.53 ± 36.81	107.11 ± 31.20
LDL-C/HDL-C	4.15 ± 2.07	0.90 ± 0.44^{b}	1.67 ± 0.99^{a}	1.55 ± 0.64^{ab}	1.11 ± 0.50^{ab}
Liver (mg/g)					
Triglyceride	158.73 ± 2.81	264.58 ± 11.16^{ab}	164.34 ± 4.89^{c}	236.93 ± 10.34^{ab}	331.22 ± 11.54^{a}
Total cholesterol	60.55 ± 2.88	173.91 ± 7.05^{a}	64.53 ± 2.55^{c}	122.38 ± 3.64^{b}	114.28 ± 2.55^{b}
Feces (mg/g)					
Triglyceride	0.58 ± 0.81	0.98 ± 0.11^{ns}	0.86 ± 0.19	0.93 ± 0.10	0.91 ± 0.11
Total cholesterol	0.96 ± 1.46	1.98 ± 0.05^{a}	1.23 ± 0.55^{ab}	1.94 ± 0.64^{a}	1.84 ± 0.55^{a}

[1] Values are mean ± S.E. of 10 measurements in each group.
Means with different superscripts within a row are significantly different ($P < 0.05$, one-way ANOVA).
NC = normal control; DC = diabetic control; DP = diabetic mice fed supplemental D-psicose; DG = diabetic mice fed supplemental D-glucose; DF = diabetic mice fed supplemental D-fructose; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; ns = not significant.

study presents evidence that dietary D-psicose can improve glucose tolerance in a transgenic model.

Effect of dietary D-psicose on serum and hepatic lipid levels and fecal lipid excretion

Serum triglyceride (TG), total cholesterol (TC), LDL-cholesterol, and HDL-cholesterol concentrations were not altered by the supplement of various sugars in *db/db* mice compared with those of diabetic control mice (Table 2). There was no significant difference in liver weight between groups (data not shown). Hepatic TG concentration was not significantly different in the D-glucose group and the slight increase was observed in the D-fructose group in diabetic model (Table 2). However, use of the D-psicose, approximately 1.4- to 2–fold, decreased hepatic TG concentration compared with that of the D-glucose or the D-fructose supplement during 28 d ($P < 0.05$, Table 2). Also, hepatic TC concentration was 2-fold lower in the D-psicose group than the other groups in *db/db* mice ($P < 0.05$, Table 2). Fecal excretion of TG and TC were not statistically different by the various sugar supplements, although they were decreased slightly in the D-psicose group compared to those of the other groups.

In the current study, dietary D-psicose lowered hepatic TG and TC remarkably, which might be related to the certain components produced by intestinal microflora in diabetes model. Matsuo and others (2003) have reported that dietary D-psicose resistant to digestion and available for colonic bacterial fermentation results in the generation of short-chain fatty acids (acetic, butyric, and propionic acids) in rats, which suggests their potential role as active components of D-psicose in hypocholesterolemic and hypolipidemic actions. This is also in good agreement with Martensson and others (2002) and Cook and Sellin (1998), described that increased bacterial activity in the large intestine results in the enhancement of bile acid deconjugation then they are not well absorbed by the gut mucosa and consequently excreted and opposed to hyperlipidemia. However, recent human studies found lack of agreement on the relation between increased colonic fermentation, lipid metabolism, and even glucose tolerance. Specifically, results were different depending on the chemical composition of the substrate source (L-rhamnose, lactulose, inulin, and so on) or the term of ingestion (acute and chronic) (Wong and Jenkins 2007).

Conclusions

This study has provided evidence that dietary D-psicose is effective in improving hyperglycemia and dyslipidemia as well as reducing weight gain in genetically determined diabetic and dyslipidemic model. The underlying mechanism may be related mainly to enhancing insulin sensitivity and improving the lipid composition. However, more studies on the mechanisms of D-psicose and clinical trials exploring whether this no-energy sweet monosaccharide could be a potent functional dietary source against pathogenic processes are needed. Consequently, D-psicose may become a highly suitable supplement in preventing obesity or postprandial glycemic control in type 2 diabetic patients.

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